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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/434,870	11/04/99	HUSE	W P-IX-3458

EXAMINER

HELMS,L

ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 03/15/01

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HM12/0315

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/434,870	Huse et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-41* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-41* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ NOTICE TO COMPLY WITH SEQUENCE REQUIREMENTS

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-41 are pending and under examination.

Claim Objections

2. Claims 6-42 are objected to because of the following informalities:

a. The numbering of claims is not in accordance with 37 CFR 1.126. The claims do not contain a claim numbered 5. Therefore, misnumbered claims 6-42 have been renumbered 5-41. Claims 13-14 depend on claims 5 and 6 respectively, claims 16-25 depend on claim 15, claims 27-34, and 36 depend on claim 26, claim 35 depends on claim 31, and claims 38-41 depend on claim 37.

b. Claim 12 is objected to because the claim contains a misspelled word "isselected". Appropriate correction is required.

Specification

3. The abstract of the disclosure is objected to because of the length of the abstract. Correction is required. See MPEP § 608.01(b).

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the oath/declaration does not list the provisional application 60/159,689 for which priority is being requested.

Sequence Requirements

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). (See for example Figure 1) However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Although this application is not in Sequence compliance an action on the merits can be performed in order to expedite compact prosecution.

Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

APPLICANT IS GIVEN THE TIME ALLOTTED IN THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply

with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

6. Claims 1-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-41 are indefinite for reciting the abbreviations "CDRs", "CDR", CDR1", "CDR2", or "CDR3"in claims 1, 2, 7, 11, 12, 15, 20, 24, 25, 26, 32, 33, 37, and 40-41. Full terminology should be in first instance of the claims followed by the abbreviation in parentheses. Dependent claims may then use the abbreviation. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

b. Claims 1-41 are indefinite for reciting "substantially the same" in claims 1, 15, and 26 because the exact meaning of the phrase is not clear. Does the phrase mean the same or not?

c. Claims 1-41 are indefinite for reciting "binding affinity substantially the same or greater than the donor CDR variable region" in claims 1, 15, and 26 because the exact meaning

of the phase is not clear. It is unclear what donor CDR variable region is being compared to. Is it the original CDRs from the donor or is it one that has a plurality of different amino acids? In addition, is the comparison of binding affinity to the same antigen or different antigen?

d. Claim 2 is indefinite because it is not clear how one is to compare the binding of a variable region to that of a CDR region.

e. Claims 1-11, 13-24, 26-32, and 34-40 are indefinite for reciting CDR amino acid positions because the exact meaning of the phrase is not clear. It is not clear if the CDRs are defined by Chothia, Kabat, or some other system. Likewise claims 6, 7, 11, 19, 20, 24 are indefinite because they recite framework regions, CDRs, or proximal to a CDR because it is not clear how these regions are defined.

f. Claim 13 recites the limitation "said altered variable regions" in claim 5 . There is insufficient antecedent basis for this limitation in the claim 5.

g. Claims 9 and 22 are indefinite for reciting "cononical framework" because the exact meaning of the phrase is not clear. It is not clear what defines the residue as "cononical".

h. Claims 13-14 and 34-35 are indefinite for reciting "wherein said altered variable regions are coexpressed with a light chain variable region" in claims 13 and 34 and reciting "wherein said altered variable regions are coexpressed with a heavy chain variable region" in claims 14 and 35 because the exact meaning of the phrases are not clear. It is not clear if the claims are intended to recite that the altered variable region if it is a heavy chain will be expressed with a light chain and visa versa. In addition it is unclear if both variable regions of a

heavy chain and a light chain are altered how these can be expressed with an additional light or heavy chain.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-14 and 26-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of optimizing the binding affinity of altered light and heavy chain variable regions of an antibody wherein one or more of the framework region amino acids from the acceptor is selected by differences in amino acid identity between donor and acceptor, or exposed to solvent, or interacts with a CDR, does not reasonably provide enablement for a method of optimizing the binding affinity of only a light chain or a heavy chain variable region of an antibody or wherein any framework region amino acid is substituted in the light or heavy chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or

guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of optimizing the activity of a catalytic antibody and a method of conferring donor CDR binding affinity and optimizing binding affinity of an antibody light chain or heavy chain variable region wherein the light or heavy chain alone would not bind antigen. The specification teaches humanization and affinity maturation of an anti-CD40 antibody (see Example 1 and Table I) wherein the antibody comprises both a heavy and light chain variable regions. The specification does not enable a method for conferring donor binding or affinity maturation of a light chain or a heavy chain alone that binds antigen or wherein any framework region amino acids are substituted.

Claims 1 and 26 are broadly drawn to antibodies which do not contain a full set of six CDRs from a light and heavy chain. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are

required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986). Thus, one skilled in the art would conclude that altering any framework region amino acids would not produce an antigen binding antibody. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of predictability in the art as evidenced by Rudikoff et al and Amit et al and the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Priority

9. The instant application claims priority to provisional application 60/159,689, filed 10/14/99. The limitations recited in claims 1-36 are supported in the 60/159,689 application, however, the limitations of a catalytic antibody and optimizing the activity of a catalytic antibody are not seen in the 60/159,689 application. Therefore, claims 1-36 are granted the priority date of 10/14/99 and claims 37-41 are granted the priority date of the instant application, 11/04/99.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-7, 12-20, 25-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Radner et al (Proc. Natl. Acad. Sci. USA 95:8910-8915, 7/1998, IDS #5.

The claims are summarized as a method of conferring donor CDR binding affinity and a method of grafting and optimizing the binding affinity of a variable region binding fragment wherein the acceptor framework region contains a plurality of different amino acids at one or

more positions, wherein the CDR is defined by Kabat, wherein the CDR contains one or more positions with a plurality of different amino acids, expressing and identifying those variable regions that have substantially similar or greater binding affinity by measuring the K(on) or K(off) from that of the parent or donor CDR variable region.

Radner et al teach a method for affinity maturation of an antibody wherein the acceptor framework has many mutations (see page 8912, bridging paragraph for left and right column) and four of the CDRs are randomized. The antibody is humanized from the parent LM609 and the antibodies produced have a binding affinity that is as good or better than the affinity of the parent antibody (see page 8914, last line in Results).

12. Claims 37-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Baca et al (Proc. Natl. Acad. Sci. USA 94:10063-10068, 9/97).

a. Claims 37-41 recite a method for optimizing the activity of a catalytic antibody variable region comprising constructing a heavy chain and light chain variable encoding nucleic acids comprising two or more CDRs as defined by Kabat with a plurality of different amino acids at one or more CDR amino acid positions and coexpressing the heavy and light chain nucleic acids and identifying variable regions by comparing transition state binding affinity.

b. Baca et al teach a phage display method of a catalytic antibody for optimizing the affinity for transition-state analog binding comprising creating a random library wherein residues

in the heavy chain and the light chain CDRs (as defined by Kabat) are mutated (see Figure 3) and wherein the antibodies are optimized to have optimized affinity for transition-state analog binding (see page 10068).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (Proc. Natl. Acad. Sci. USA 95:6037-6042, 5/1998, IDS #5) and further in view of Baca et al (The Journal of Biological Chemistry 272:10678-10684, 1997) and Yelton et al (J. Immunol 155:1994-2004, 1995, IDS#5) and Studnicka et al (Protein Engineering 7:805-814, 1994, IDS #5).

The claims are summarized as a method of conferring donor CDR binding affinity and a method of grafting and optimizing the binding affinity of a variable region binding fragment wherein the acceptor framework region contains a plurality of different amino acids at one or more positions selected by differences in amino acid identity between donor and acceptor, being in a cononical framework, solvent exposed, predicted to be proximal to a CDR, wherein the CDR is defined by Kabat, wherein the CDR contains one or more positions with a plurality of different amino acids, expressing and identifying those variable regions that have substantially similar or greater binding affinity by measuring the K(on) or K(off) from that of the parent or donor CDR variable region.

Wu et al teach a method of affinity maturation of an antibody with w phage display library comprising providing a library wherein residues in all six CDRs are randomized with all 20 amino acids and the mutants are screened by determining the binding affinity by measuring k(on) and k(off) (see abstract and Materials and Methods). Wu et al does not teach random

mutagenesis of framework regions, or methods of selecting framework regions to alter. These deficiencies are made up for in the teachings of Baca et al, Yelton et al, and Studnicka et al.

Baca et al teach a method of humanization with improved binding affinity comprising providing a random library wherein framework region residues contain many different possible amino acids at several positions. Baca et al also teach determination of the binding affinity by determining association and dissociation rate constants. Baca et al also teach the reason to change framework residues (see page 10678-9).

Yelton et al teach a method of affinity maturation of an antibody comprising mutations in the CDRs of the antibody. Yelton et al also teach determining increases in binding affinity by determining k(on) and k(off). Yelton et al also teach that framework residues may also be altered and framework residues may contribute to improved affinity (see page 2001).

Studnicka et al teach a method of humanization comprising altering framework residues and the parameters and criteria for determining which residues to alter (see page 808-812).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have combined the teachings of Wu et al, Baca et al, Yelton et al, and Studnicka et al to produce a method of conferring donor CDR binding affinity or optimizing the binding affinity of an antibody comprising mutagenizing CDRs and framework region residues.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Wu et al, Baca et al, Yelton et al, and

Studnicka et al to produce a method of conferring donor CDR binding affinity or optimizing the binding affinity of an antibody comprising mutagenizing CDRs and framework region residues because Wu et al teach a method of affinity mutation comprising providing a library of multiple mutations in the CDRs and "it has been demonstrated that individual mutations can be combined to further enhance antibody affinity" (see page 6039). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Wu et al, Baca et al, Yelton et al, and Studnicka et al to produce a method of conferring donor CDR binding affinity or optimizing the binding affinity of an antibody comprising mutagenizing CDRs and framework region residues because Baca et al teach a method of affinity maturation comprising multiple mutations in the framework regions and Yelton et al teach affinity maturation with mutations in the CDRs and "altering framework residues may contribute to improved affinity" (see page 2001 of Yelton et al). Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Wu et al, Baca et al, Yelton et al, and Studnicka et al to produce a method of conferring donor CDR binding affinity or optimizing the binding affinity of an antibody comprising mutagenizing CDRs and framework region residues because Studnicka et al teach a method of humanization comprising altering framework residues based on several criteria to produce antibodies that retain, when humanized, the antigen binding and affinity of the parent antibody. Thus, it would have been obvious to one on ordinary skill in the art to not only mutagenize the CDRs as Wu et al and Yelton et al did but to combine this with the teachings of

Baca et al and Studnicka et al in the mutagenesis of framework residues in combination with CDR residues to increase antibody binding affinity.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

SHEELA HUFF
PRIMARY EXAMINER

Application No.: 09/434870

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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